With respect to claim 20, and claims depending therefrom, the Action takes the position that claim 20 should be rewritten with positive steps in proper method format. Applicants have amended claim 20, which has been recast with positive methods steps, set forth in the gerundial. No additional limitations have been placed into the claim and it is believed that the claim now bears precisely the same scope as the unamended claim. If the Examiner disagrees, Applicants would appreciate the Examiner to state in what way it is believed that the claim has in any way been narrowed so that Applicants can revise the claim to ensure that its scope has not been narrowed.

The Action next takes the position that claim 3 is indefinite in its use of the negative phrase "non-genomic." In response, Applicants are firmly of the position that "non-genomic" would be clear and definite to one of ordinary skill in the art. As explained in the enclosed dictionary page, the term "genomic" is a contraction of the words "gene" and "chromosome," and refers to all of the *chromosomal* DNA complement of a given cell. Therefore, non-genomic DNA is any DNA that is not derived from the chromosome complement. Thus, it is well understood that chloroplast and mitochondrial DNA are non-chromosomal, as is cDNA.

Claims 72-73 and 75 are next identified by the Action as confusing, and Applicants have amended these claims slightly in a manner that is believed to clear up the confusion, as it is now clear that each of these claims now concern application of amplification to two different DNA samples, which was what was originally intended that these claims cover. As such, it is not believed that the scope of these claims has been in any way narrowed by these amendments.

With respect to claims 50-51, Applicants have amended these claims in a manner consistent with the underlying BioStar and Luminex technology, as employed by the Examiner in the obviousness rejections of these claims, and thus should be acceptable.

It is submitted that the claims are free of any section 112, second paragraph, concerns.

III. Rejection of Claims 87-89 Under Section 102(b)

The Action next takes the position that the subject matter of claims 87-89 are anticipated by the Boehringer catalogue, at page 95. Applicants respectfully traverse.

Claims 87-89, as originally filed, required that the 5' end of the molecule contain a sequence for annealing to a primer. As such, it would be necessary that the 5' end have a predetermined sequence – to permit one to prepare a primer that can be used to, for example, amplify the sequence. Claims 87 and 88 have been amended to clarify that this was the intended meaning of the 5' sequence limitations contained in the claims as filed. It is clear from the Boehringer catalogue that the DNA molecules to which it refers do not have a predetermined sequence at their 5' ends.

IV. Rejection of Claims 4, 20, 21, 23, 24, 27, 28, 29, 36-42, 44, 45, 48, 57, 58, 59 and 85 as Obvious Over Lizardi *et al.* in view of Kambara *et al.*

The Action next rejects claims 4, 20, 21, 23, 24, 27, 28, 29, 36-42, 44, 45, 48, 57, 58, 59 and 85 as Obvious Over Lizardi *et al.* in view of Kabara *et al.* The Action takes the position that Lizardi teaches hybridizing a primer comprising a sequence complementary to the known sequence portion of a DNA to be amplified, and thereby amplifying the DNA. Lizardi is also said to teach various aspects of the dependent claims. However, the Action recognizes that Lizardi fails to teach that the primer are complementary to the linker sequence at their 5' end and that the primer comprises a specificity region. The Action concludes by positing that Kambara teaches primers having these two elements. Applicants respectfully traverse.

An aspect of the present invention is the placement of two different linker sequences at the opposite ends of the DNA molecule that is to be analyzed. However, neither reference relied

upon by the Examiner provides either a motivation or a means for obtaining a *different* linker sequence on both ends of the target DNA molecule. The means for achieving a different linker at each end is not particularly straightforward. One way it may be achieved is by, *first*, digesting a DNA molecule with a first restriction enzyme, and adding the same linker to both ends, *then*, digesting the DNA molecule with a second restriction enzyme to remove the linker from one end, following by adding a second linker to the second end. See, *e.g.*, specification page 8, lines 15 *et seq*. In contrast, it does not appear that the approaches that we have been able to identify in Kambara or Lizardi would result in a different linker sequence at opposing ends being added. For example, the paragraph at col. 2, lines 37-61 would appear to teach the same linker sequence being added to both ends. This interpretation is confirmed by reference to Figure 1, which in fact shows the same linker sequence being added to both ends, and by reference to the discussion at col. 6.

Lizardi is apparently even further removed. It appears as though Lizardi is concerned with linkers in the context of preparing concatenates of DNA. See, *e.g.*, Lizardi at cols. 11-12. Although it is difficult to determine from Lizardi just what it does teach, it appears as though Lizardi teaches concatenation of DNA with linkers that does not necessarily result in molecules having different linker sequences at opposing ends. For example, in the paragraph bridging columns 21 and 22, it appears that Lizardi simply teaches linkers in the form of A and T duplexes on either side of the concatenated DNA—thus, both ends will have the same sequence. The same can be said of the description of linker-concatenated DNA beginning at line 13, column 22, and shown in Figure 4. Moreover, even if there is some suggestion in Lizardi to employ more than one linker, we have been unable to find any teaching in Lizardi that would

teach one how to ensure that a different linker would be added to opposing ends of the target sequence.

It is submitted that based on the foregoing, the Examiner has failed to make out a *prima facie* case of obviousness of the claims that are the subject of the present rejection. If the Examiner is aware of any specific disclosure in either of these or other references that relates to the insufficiencies in the art noted above, or that would otherwise give rise to a *prima facie* rejection, the Examiner is requested to indicate clearly on the record where such a teaching or suggestion can be found.

V. Rejection of Claim 3 Obvious Over Lizardi *et al.* in view of Kambara et al., further in view of Leushner

The Action next rejects claim 3 as obvious over the same combination of references discussed above as applied to claim 20, further in view of Leushner, which is said to teach the sequencing of non-genomic DNA.

In response, Applicants first incorporate by reference the arguments set forth above to the main claim, claim 20, which are applicable to any claim depending from claim 20, such as the instant claim 3. Furthermore, the Examiner is reminded that for references to be properly combinable there must be some motivation to combine that is either explicitly or implicitly set forth in the references themselves. Here, the Examiner has failed to identify any basis for combining these references, other than the fact that they both relate to DNA, which certainly can not be enough for proper combinability.

Furthermore, even if the references are properly combinable, the combination nevertheless does not obviate the invention of claim 3. Claim 3 limits the method of claim 20 to the use of non-genomic DNA, where the non-genomic DNA is the DNA that contains the special

dissimilar linker sequences on its two ends and which is subject to a DNA polymerization reaction using the two specialized primers. Yet, it is not believed that Leushner says anything about the applicability of non-genomic DNA to such an approach, and certainly makes no suggestion to undertake such a linker-addition.

When the teachings of Leushner is combined with that of, for example, Lizardi, the combination is even further removed for the subject matter of claim 3. For example, the exemplary "non-genomic" DNA of Lizardi is cDNA—yet, as noted above, Lizardi teaches to add a precisely the same linker to both ends of cDNA, a poly stretch of "A"s and "T"s, rather than two different linkers. See, e.g., Lizardi, paragraph bridging columns 21 and 22.

The same can be said of Kambara as well, which also teaches that the same linker be applied to both ends of the target sequence.

The rejection of claim 3 should therefore be reconsidered and withdrawn.

VI. Rejection of Claims 46, 71-74, 76 and 86 as Obvious Over Lizardi *et al.* in view of Kambara *et al.*, and further in view of Black

The Action next rejects claims 46, 71-74, 76 and 86 as obvious over Lizardi and Kambara for the reasons stated above, further in view of Black. The Action takes the position that Black teaches multiple sources for DNA sequences for sequencing and teaches the use of polyacrylamide gel electrophoresis.

In response, Applicants first incorporate by reference the arguments set forth above to the main claim, claim 20, which are applicable to any claim depending from claim 20, such as the instant claims 46, 71-74, 76 and 86. Furthermore, the Examiner is reminded that for references to be properly combinable there must be some motivation to combine that is either explicitly or implicitly set forth in the references themselves. Here, the Examiner has failed to identify any

basis for combining these references. Black relates to a very specific problem, that of providing a specific type of polynucleotide or polypeptide, the so-called "MurC" sequences, and diagnostic applications. The excerpt relied upon by the Examiner, at columns 21-22, merely relate to diagnosing the presence of MurC sequences, or mutations in the sequences, in DNA or other samples. How this teaching is combinable with the subject matter of Lizardi and/or Kambara is not clear on this record.

Even if the references are properly combinable, the combination nevertheless does not obviate the invention of the instantly rejected claims. These claims all limit the method of claim 20, and Black in no way addresses the shortcomings noted above with respect to Lizardi and Kambara. On the contrary, Black actually teaches you to remove sequences from the 3' end of primers, rather than adding sequences (see, e.g., col. 22, lines 34-43). Furthermore, it does not appear as though Black teaches or suggests that the DNA that is subject to analysis should be modified to contain the special dissimilar linker sequences on its two ends and which is subject to a DNA polymerization reaction using the two specialized primers.

The rejection of claims 46, 71-74, 76 and 86 should therefore be reconsidered and withdrawn.

VII. Rejection of Claim 47 as Obvious Over Lizardi *et al.* in view of Kambara et al., further in view of Karger

The Action next rejects claim 47 as obvious over the same combination of references discussed above as applied to claim 20, further in view of Karger, which is said to teach the analysis of products by capillary gel electrophoresis.

In response, Applicants first incorporate by reference the arguments set forth above to the main claim, claim 20, which are applicable to any claim depending from claim 20, such as the

instant claim 47. Furthermore, the Examiner is reminded that for references to be properly combinable there must be some motivation to combine that is either explicitly or implicitly set forth in the references themselves. Here, the Examiner has failed to identify any basis for combining the teachings of Karger with those of the primary references. It appears as though the Examiner has merely picked a reference out of the prior art that relates to capillary gel electrophoresis and attempted to combine that teachings with the primary references without a proper combinability analysis.

Even if the references are properly combinable, the combination nevertheless does not obviate the invention of the instantly rejected claims. Claim 47 limits the method of claim 20 to the use of capillary electrophoresis *in the context of the method of claim 20*, and Karger in no way addresses the shortcomings noted above with respect to Lizardi and Kambara. That is, Karger in no way teaches or suggests that the DNA that is subject to analysis in the methods of, for example, Kambara or Lizardi, should be modified to contain the special dissimilar linker sequences on its two ends and which is subject to a DNA polymerization reaction using the two specialized primers.

The rejection of claim 47 should therefore be reconsidered and withdrawn.

VIII. Rejection of Claim 49 as Obvious Over Lizardi *et al.* in view of Kambara *et al.*, further in view of Winger *et al.*

The Action next rejects claim 49 as obvious over the same combination of references discussed above as applied to claim 20, further in view of Winger, which is said to teach the use of a reporter and quencher fluorescent dye for use in PCR assays.

In response, Applicants first incorporate by reference the arguments set forth above to the main claim, claim 20, which are applicable to any claim depending from claim 20, such as the

instant claim 49. Furthermore, the Examiner is reminded that for references to be properly combinable there must be some motivation to combine that is either explicitly or implicitly set forth in the references themselves. Here, the Examiner has failed to identify any basis for combining the teachings of Winger with those of the primary references.

Even if the references are properly combinable, the combination nevertheless does not obviate the invention of the instantly rejected claims. Claim 49 limits the method of claim 20 to the analysis of the DNA polymerization method of claim 20 using energy transfer. Yet, Winger clearly fails to in any way address the shortcomings noted above with respect to Lizardi and Kambara. That is, Winger in no way teaches or suggests that the DNA that is subject to analysis in the methods of, for example, Kambara or Lizardi, should be modified to contain the special dissimilar linker sequences on its two ends and which is subject to a DNA polymerization reaction using the two specialized primers.

The rejection of claim 49 should therefore be reconsidered and withdrawn.

IX. Rejection of Claim 50 as Obvious Over Lizardi *et al.* in view of Kambara *et al.*, further in view of Crosby

The Action next rejects claim 50 as obvious over the same combination of references discussed above as applied to claim 20, further in view of Crosby, which is said to teach the analysis of products using the Biostar technology.

In response, Applicants first incorporate by reference the arguments set forth above to the main claim, claim 20, which are applicable to any claim depending from claim 20, such as the instant claim 50. Furthermore, the Examiner is reminded that for references to be properly combinable there must be some motivation to combine that is either explicitly or implicitly set

forth in the references themselves. Here, the Examiner has failed to identify any basis for combining the teachings of Crosby with those of the primary references.

Even if the references are properly combinable, the combination nevertheless does not obviate the invention of the instantly rejected claims. Claim 50 limits the method of claim 20 to the analysis of the DNA polymerization method of claim 20 using the Biostar technology. Yet, Crosby clearly fails to in any way address the shortcomings noted above with respect to Lizardi and Kambara. That is, Crosby in no way teaches or suggests that the DNA that is subject to analysis in the methods of, for example, Kambara or Lizardi, should be modified to contain the special dissimilar linker sequences on its two ends and which is subject to a DNA polymerization reaction using the two specialized primers.

The rejection of claim 50 should therefore be reconsidered and withdrawn.

X. Rejection of Claim 51 as Obvious Over Lizardi *et al.* in view of Kambara *et al.*, further in view of Chandler

The Action next rejects claim 50 as obvious over the same combination of references discussed above as applied to claim 20, further in view of Chandler, which is said to teach the analysis of products using the Luminex technology.

In response, Applicants first incorporate by reference the arguments set forth above to the main claim, claim 20, which are applicable to any claim depending from claim 20, such as the instant claim 51. Furthermore, the Examiner is reminded that for references to be properly combinable there must be some motivation to combine that is either explicitly or implicitly set forth in the references themselves. Here, the Examiner has failed to identify any basis for combining the teachings of Chandler with those of the primary references.

Even if the references are properly combinable, the combination nevertheless does not obviate the invention of the instantly rejected claims. Claim 51 limits the method of claim 20 to the analysis of the DNA polymerization method of claim 20 using the Lumiex approach. Yet, Chandler clearly fails to in any way address the shortcomings noted above with respect to Lizardi and Kambara. That is, Chandler in no way teaches or suggests that the DNA that is subject to analysis in the methods of, for example, Kambara or Lizardi, should be modified to contain the special dissimilar linker sequences on its two ends and which is subject to a DNA polymerization reaction using the two specialized primers.

The rejection of claim 51 should therefore be reconsidered and withdrawn.

XI. Rejection of Claims 52 and 55 as Obvious Over Lizardi *et al.* in view of Kambara *et al.*, further in view of Higuchi

The Action next rejects claims 52 and 55 as obvious over the same combination of references discussed above as applied to claim 20, further in view of Higuchi, which is said to teach quantitative PCR using real-time amplification.

In response, Applicants first incorporate by reference the arguments set forth above to the main claim, claim 20, which are applicable to any claim depending from claim 20, such as the instant claims 52 and 55. Furthermore, the Examiner is reminded that for references to be properly combinable there must be some motivation to combine that is either explicitly or implicitly set forth in the references themselves. Here, the Examiner has failed to identify any basis for combining the teachings of Higuchi with those of the primary references.

Even if the references are properly combinable, the combination nevertheless does not obviate the invention of the instantly rejected claims. Claims 52 and 55 limit the method of claim 20. Yet, Higuchi clearly fails to in any way address the shortcomings noted above with

respect to Lizardi and Kambara. That is, Higuchi in no way teaches or suggests that the DNA that is subject to analysis in the methods of, for example, Kambara or Lizardi, should be modified to contain the special dissimilar linker sequences on its two ends and which is subject to a DNA polymerization reaction using the two specialized primers.

The rejection of claims 52 and 55 should therefore be reconsidered and withdrawn.

XII. Rejection of Claims 53-54 as Obvious Over Lizardi *et al.* in view of Kambara *et al.*, Higuchi and further in view of Rein

The Action next rejects claims 53-54 as obvious over the same combination of references discussed above as applied to claims 52 and 55 above, further in view of Rein, which is said to teach the quantification of amplification products.

In response, Applicants first incorporate by reference the arguments set forth above to the main claim, claim 20, which are applicable to any claim depending from claim 20, such as the instant claims 53-54. Furthermore, the Examiner is reminded that for references to be properly combinable there must be some motivation to combine that is either explicitly or implicitly set forth in the references themselves. Here, the Examiner has failed to identify any basis for combining the teachings of Rein with those of the primary references. It is noted that Rein relates to a specific invention, the selection of oligonucleotides that selectively bind retroviral nucleocapsid proteins, and does not appear to relate *per se* to DNA analytical methods.

Even if the references are properly combinable, the combination nevertheless does not obviate the invention of the instantly rejected claims. Claims 53-54 limit the method of claim 20. Yet, Rein clearly fails to in any way address the shortcomings noted above with respect to Lizardi and Kambara. That is, Rein in no way teaches or suggests that the DNA that is subject to analysis in the methods of, for example, Kambara or Lizardi, should be modified to contain the

special dissimilar linker sequences on its two ends and which is subject to a DNA polymerization reaction using the two specialized primers.

The rejection of claims 53-54 should therefore be reconsidered and withdrawn.

XIII. Rejection of Claims 56 and 26 as Obvious Over Lizardi *et al.* in view of Kambara *et al.*, further in view of Duchamel

The Action next rejects claims 56 and 26 as obvious over the same combination of references discussed above as applied to claims 45 and 21, which depend from 20, further in view of Duchamel, which is said to teach the analysis of products using multi-well plates.

In response, Applicants first incorporate by reference the arguments set forth above to the main claim, claim 20, which are applicable to any claim depending from claim 20, such as the instant claims 56 and 26. Furthermore, the Examiner is reminded that for references to be properly combinable there must be some motivation to combine that is either explicitly or implicitly set forth in the references themselves. Here, the Examiner has failed to identify any basis for combining the teachings of Duchamel with those of the primary references. It is, for example, noted that Duchamel is concerned with the specific problem of the detection of nucleotide sequences of *Serpulina hyodysenteriae*, and it is unclear how it relates *per se* to the subject matter of the present invention.

Even if the references are properly combinable, the combination nevertheless does not obviate the invention of the instantly rejected claims. Claims 56 and 26 ultimately limit the method of claim 20. Yet, Duchamel clearly fails to in any way address the shortcomings noted above with respect to Lizardi and Kambara. That is, Duchamel in no way teaches or suggests that the DNA that is subject to analysis in the methods of, for example, Kambara or Lizardi,

should be modified to contain the special dissimilar linker sequences on its two ends and which is subject to a DNA polymerization reaction using the two specialized primers.

The rejection of claims 56 and 26 should therefore be reconsidered and withdrawn.

XIV. Rejection of Claims 60-61 as Obvious Over Lizardi *et al.* in view of Kambara *et al.*, further in view of Stoler

The Action next rejects claims 60-61 as obvious over the same combination of references discussed above as applied to claim 20, further in view of Stoler, which is said to teach comparing sequences from different tissues.

In response, Applicants first incorporate by reference the arguments set forth above to the main claim, claim 20, which are applicable to any claim depending from claim 20, such as the instant claims 60-61. Furthermore, the Examiner is reminded that for references to be properly combinable there must be some motivation to combine that is either explicitly or implicitly set forth in the references themselves. Here, the Examiner has failed to identify any basis for combining the teachings of Stoler with those of the primary references.

Even if the references are properly combinable, the combination nevertheless does not obviate the invention of the instantly rejected claims. Claims 60-61 ultimately limit the method of claim 20. Yet, Stoler clearly fails to in any way address the shortcomings noted above with respect to Lizardi and Kambara. That is, Stoler in no way teaches or suggests that the DNA that is subject to analysis in the methods of, for example, Kambara or Lizardi, should be modified to contain the special dissimilar linker sequences on its two ends and which is subject to a DNA polymerization reaction using the two specialized primers.

The rejection of claims 60-61 should therefore be reconsidered and withdrawn.

XV. Rejection of Claim 25 as Obvious Over Lizardi *et al.* in view of Kambara *et al.*, further in view of Lockhart

The Action next rejects claim 25 as obvious over the same combination of references discussed above as applied to claim 20, further in view of Lockhart, which is said to teach the identification of products using computer technology.

In response, Applicants first incorporate by reference the arguments set forth above to the main claim, claim 20, which are applicable to any claim depending from claim 20, such as the instant claim 25. Furthermore, the Examiner is reminded that for references to be properly combinable there must be some motivation to combine that is either explicitly or implicitly set forth in the references themselves. Here, the Examiner has failed to identify any basis for combining the teachings of Lockhart with those of the primary references.

Even if the references are properly combinable, the combination nevertheless does not obviate the invention of the instantly rejected claims. Claim 25 limits the method of claim 20 to the analysis of the DNA polymerization method of claim 20. Yet, Lockhart clearly fails to in any way address the shortcomings noted above with respect to Lizardi and Kambara. That is, Lockhart in no way teaches or suggests that the DNA that is subject to analysis in the methods of, for example, Kambara or Lizardi, should be modified to contain the special dissimilar linker sequences on its two ends and which is subject to a DNA polymerization reaction using the two specialized primers.

The rejection of claim 25 should therefore be reconsidered and withdrawn.

XVI. Rejection of Claim 43 as Obvious Over Lizardi *et al.* in view of Kambara *et al.*, in view of Mathies and in view of Ward

The Action lastly rejects claim 43 as obvious over the same combination of references discussed above as applied to claim 20, further in view of Mathies and Ward, which are said to modified primers.

In response, Applicants first incorporate by reference the arguments set forth above to the main claim, claim 20, which are applicable to any claim depending from claim 20, such as the instant claim 43. Furthermore, the Examiner is reminded that for references to be properly combinable there must be some motivation to combine that is either explicitly or implicitly set forth in the references themselves. Here, the Examiner has failed to identify any basis for combining the teachings of Mathies and Ward with each other and with the those of the primary references.

Even if the references are properly combinable, the combination nevertheless does not obviate the invention of the instantly rejected claims. Claim 43 limits the method of claim 20. Yet, Mathies and Ward, alone or in combination, clearly fails to in any way address the shortcomings noted above with respect to Lizardi and Kambara. That is, these references in no way teaches or suggests that the DNA that is subject to analysis in the methods of, for example, Kambara or Lizardi, should be modified to contain the special dissimilar linker sequences on its two ends and which is subject to a DNA polymerization reaction using the two specialized primers.

The rejection of claim 43 should therefore be reconsidered and withdrawn.

XVII. Conclusion

It is submitted that the present response is a complete response to the outstanding official action, and that the claims are in condition for allowance. If the Examiner has any questions or comments, a telephone call to the undersigned at (512) 536-3055 is requested.

Respectfully submitted,

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CLAIM AMENDMENTS

20. A method of subjecting a DNA molecule to a DNA synthesis reaction, comprising the steps of:

a) obtaining a ~~the~~ DNA molecule having a first linker sequence positioned at one end of the DNA molecule and a second linker sequence, different from said first linker sequence, positioned at the other end of the DNA molecule; and

b) subjecting ~~, wherein~~ said DNA ~~is subjected~~ to a DNA synthesis reaction with a primer set comprising:

~~a~~i) a first primer, wherein the 5' sequence of said primer is complementary to said first linker sequence and the 3' sequence of said primer comprises a specificity region; and

~~b~~ii) a second primer, wherein the 5' sequence of said primer is complementary to said second linker sequence and the 3' sequence of said primer comprises a specificity region.

50. The method of claim~~,~~ 45, wherein said analysis of products is by a~~the BioStar~~ filtration and extraction device~~technology~~.

51. The method of claim 45, wherein said analysis of products is by the use of interlaced lasers and multiple fluorescent measurements~~Luminex technology~~.

71. The method of claim 20, performed on more than one sample of DNA, wherein the DNA samples are derived from a cell or tissue type obtained from ~~a~~ different species.

72. The method of claim 20, performed on more than one sample of DNA, wherein the DNA samples are derived from a cell or tissue type obtained from ~~a~~ different organisms.

73. The method of claim 20, performed on more than one sample of DNA, wherein the DNA samples are derived from a cell or tissue at different stages of development.

74. The method of claim 20, performed on more than one sample of DNA, wherein the DNA samples are derived from a normal cell or tissue and ~~on the DNA~~ derived from a cell or tissue that is diseased.

75. The method of claim 20, performed on more than one sample of DNA, wherein the DNA samples are derived from a cell or tissue cultured in vitro under different conditions.

87. A primer molecule having (a) a predetermined 5' sequence for annealing to a linker sequence and (b) a 3' terminal specificity region of from 3 to 8 nucleotides in length, the specificity region defined as one of all possible sequence combinations of A, T, G and C.

88. A population of primer molecules, the primer molecules having (a) a predetermined 5' sequence for annealing to a linker sequence and (b) a 3' terminal specificity region of from 3 to 8 nucleotides in length, the population of primer molecules having specificity regions collectively reflecting all possible sequence combinations of A, T, G and C.